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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Singer *et al.*

Application No.: 10/773,535 Group Art Unit: 1625

Filed: February 5, 2004 Examiner: Morris, Patricia L

For: Method of Stabilizing Lansoprazole

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DECLARATION UNDER 37 C.F.R. § 1.132

I, CLAUDE SINGER, Ph.D., of 8/8 David Elazar, Kfar Saba 44358, Israel, declare and state as follows:

I. BACKGROUND

1. I am a named co-inventor of U.S. application Serial No. 10/773,535 ("the '535 application") filed February 5, 2004.

2. I received my Ph.D. degree in 1985 from The Polythehnic Institute Bucharest, Rumania. Since 1986, I have worked for Teva Pharmaceutical Industries, Ltd. ("Teva"). I am currently Teva's API Global R&D Management. In that position, I am responsible for Global R&D Project Coordination.

3. I have reviewed and understood the specification and the claims of U.S. patent application Serial No. 10/773,535 entitled "A Method for the Purification of Lansoprazole".

4. I am familiar with the prosecution of the '535 application and have reviewed and understood the Office Actions mailed October 9, 2008 and July 14, 2009 ("the Office Actions"). The Office Actions allege that lansoprazole as disclosed in various patents, including U.S. Pat. No. 4,628,098 ("Nohara *et al.*"), and published applications WO 01/21617 ("Choi *et al.*") and US 2003/0036554 ("Avrutov *et al.*", now U.S. Pat. No. 7,129,358), anticipates or renders obvious claims 33-38, 42-45, and 54-55 of the present application.

5. I have reviewed and understood U.S. Patent No. 4,628,098 issued on December 9, 1989, to Nohara *et al.*, ("the '098 patent"), and the publications WO 01/21617 published on March 29, 2001, to Choi et al., ("the '617 publication") and US 2003/0036554 published on February 20, 2003, to Avrutov et al., ("the '554 publication", which issued on October 31, 2006 as U.S. Pat. No. 7,129,358 ("the '358 patent")).

II. PREPARATION OF LANSOPRAZOLE ACCORDING TO THE '098 AND '358 PATENTS AND THE '617 PUBLICATION

6. I have directly supervised the repetition of the preparations of lansoprazole according to Example 2 of the '098 patent, Examples 3 and 10 of the '358 patent, and Example 1 and Comparative Examples 1 - 3 of the '617 publication. These repetitions of preparing lansoprazole are as follows.

7. The repetition of Example 2 of the '098 patent was carried out as follows. To a solution of 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole (10 g) (TFPB) in chloroform (105 ml) was added dropwise under ice-cooling (2°C) over a period of 30 minutes m-chloroperbenzoic acid (5.9 g) dissolved in chloroform (80 ml) and stirred for 1/2 hour at 2°C and the resulting material was analyzed by HPLC to

determine completion of the reaction. To the solution was added a saturated aqueous solution of sodium hydrogen carbonate and the organic phase was separated, then dried on magnesium sulfate, filtered, 250g Silicagel was added and the suspension was concentrated (evaporated to residue). The residue was chromatographed on a column of silica gel (250 g), eluted with ethyl acetate and the ethylacetate solution was evaporated to dryness. The residue was recrystallized from acetone-isopropyl ether (25:25 ml) by heating to reflux, adding acetone (50 ml) to obtain a clear solution, and cooling to 0°C. The material was filtered and washed with acetone-isopropylether (10:10 ml) and dried to give a material that was given identifier KC-P-067.

8. The repetition of Example 3 of the '358 patent was carried out as follows. 7.5 mg VO $(acac)_2$ was dissolved in 60 ml ethanol at room temperature. The solution was stirred and 15 grams of 2-[[[3-methyl-4-(2,2,2-trifluoro-ethoxy)-2-pyridinyl]methyl]thio]-1H-benz-imidazole were added and cooled to 16-17°C. 7.5 ml aqueous tert-butyl hydroperoxide (TBHP) was added over a 5-minute period at 16-17°C and the solution was then stirred for 3 hours. After completion of the reaction, and the remaining product mixture was cooled to about 15°C and treated with aqueous sodium metabisulphite. The resultant solid was filtered off, washed with cooled ethyl acetate, and dried at 40°C under vacuum for 18 hours, to afford the end product given the identifier KC-P-071.

9. The repetition of Example 10 of the '358 patent was carried out as follows. A mixture of 10 grams 2-[[[3-methyl-4-(2,2,2-trifluoro-ethoxy)-2-pyridinyl]methyl]thio]-H-benzi- midazole, 10 grams $NaHCO_3$ and 66 ml aqueous methanol (50%) was cooled to -2°C and 11.67 grams of Oxone® was added. The mixture was stirred for 4 hours at 0°C and the resulting material was analyzed by HPLC to determine completion of this reaction. A further 3.33 gram Oxone® was added and stirred for another 1.5 hours and the resulting material was analyzed by HPLC to determine completion of this reaction. A solution of 2.67 grams

sodium metabisulfite in 67 ml water was added dropwise over 10 minutes. After further stirring the resultant precipitate was filtered, washed 50% aqueous methanol and dried to obtain material given identifier KC-P-065.

10. The repetition of Example 1 of the '617 publication was carried out as follows. 3 g of 2- [[3-methyl-4- trifluoroethoxy] pyrid-2-yl] methylthio] benzimidazole was dissolved in 60 ml of 95% ethanol and cooled to a temperature of -20 to -30°C (-24°C for procedure KC-P-072). Then, 79.2 mg of methyltrioxo rhenium and 0.93 g of a 30% aqueous hydrogen peroxide solution were added, and stirred for 5 hours at the same temperature and the resulting material was analyzed by HPLC to monitor the completion of the reaction. To the reaction mixture produced was added an aqueous sodium thiosulfate solution (3 g/30 ml) and then stirred for 1 hour while cooling with ice. The reaction mixture was filtered and washed with an ice-cooled isopropanol: water mixture (10 ml: 10 ml), and then dried under vacuum at 40°C for 18 hours to obtain material given identifier KC-P-072.

11. The repetition of Comparative Example 1 of the '617 publication was carried out as follows. 3 g of 2- [[3-methyl-4- trifluoroethoxy] pyrid-2-yl] methylthio] benzimidazole was dissolved in 30 ml of 95% methanol and cooled to a temperature of -20°C (reaction mixture froze). Then, 79.2 mg of methyltrioxorhenium and 0.93 g of an aqueous 30% hydrogen peroxide solution were added, and stirred for 5 hours at the same temperature and the resulting material was analyzed by HPLC to monitor the completion of the reaction. To the reaction mixture produced was added an aqueous sodium thiosulfate solution (3 g/30 ml) and isopropanol (30 ml), and then stirred for 1 hour while cooling with ice. The reaction mixture was filtered and washed with an ice-cooled isopropanol: water mixture (10: 10 ml), and then dried under vacuum at 40°C for 18 hours to obtain material given identifier KC-P-069.

12. The repetition of Comparative Example 2 of the '617 publication was carried out as follows. 3 g of 2- [[3-methyl-4- trifluoroethoxy] pyrid-2-yl] methylthio] benzimidazole was dissolved in 60 ml of an ethanol: water mixture (1: 1) and cooled to a temperature of-20°C (reaction mixture froze). Then, 79.2 mg of methyltrioxorhenium and 0.93 g of an aqueous 30% hydrogen peroxide solution were added, and stirred for 5 hours at the same temperature and the resulting material was analyzed by HPLC to monitor the completion of the reaction. To the reaction mixture produced was added an aqueous sodium thiosulfate solution (3 g/30 ml) and isopropanol (30 ml), and then stirred for 1 hour while cooling with ice. The reaction mixture was filtered and washed with an ice-cooled isopropanol: water mixture (10: 10 ml), and then dried under vacuum at 40°C for 18 hours to obtain material given identifier KC-P-070.

13. The repetition of Comparative Example 3 of the '617 publication was carried out as follows. 3 g of 2- [[3-methyl-4- trifluoroethoxy] pyrid-2-yl] methylthio] benzimidazole was dissolved in 60 ml of 95% ethanol and cooled to a temperature of -20°C. Then, 9.9 mg of methyltrioxorhenium and 0.93 g of an aqueous 30% hydrogen peroxide solution were added, and stirred for 5 hours at the same temperature and the resulting material was analyzed by HPLC to monitor the completion of the reaction. To the reaction mixture produced was added an aqueous sodium thiosulfate solution (3 g/30 ml) at 0°C and followed by the addition of isopropanol (30 ml), and then stirred for 1 hour while cooling with ice. The reaction mixture was filtered and washed with an ice-cooled isopropanol: water mixture (10: 10 ml), and then dried under vacuum at 40°C for 18 hours to obtain material given identifier KC-P-073.

III. ANALYSIS OF LANSOPRAZOLE ACCORDING TO THE '098 AND '358 PATENTS AND THE '617 PUBLICATION

14. The impurity profile was determined using the HPLC USP method analysis for the examples obtained according to the various methods of preparing lansoprazole in the '098 and '358 patents and the '617 publication, as shown in Table 1.

Table 1: Impurity Profile of Lansoprazole Prepared According to the '098 and '358 patents and the '617 publication.

Reference		Sample	Impurity profile in percent (w/w)					
			Impurity D	Impurity E	LNP-NO	LNP-SO_2	TFPB	LNP
US 4,628,098 Ex 2		KC-P-067				0.306	1.843	97.746
US 7,129,358	Ex 3	KC-P-071	0.030	0.017	0.018	2.606	21.875	75.385
	Ex 10	KC-P-065			2.268	31.154	40.378	20.179
WO 01/21617	Ex 1	KC-P-072			0.235	0.040	10.038	89.556
	Comp Ex 1	KC-P-069					61.040	38.592
	Comp Ex 2	KC-P-070				0.055	98.693	1.080
	Comp Ex 3	KC-P-073					98.451	1.549

In the above table Impurity D, Impurity E, LNP-NO, LNP-SO_2, and TFPB represent the most common impurities of Lansoprazole, LNP-SO_2 being the sulfone impurity and TFPB the sulfide impurity.

15. It is my opinion, that each of the Lansoprazole samples KC-P-067, KC-P-071, KC-P-065, KC-P-068, KC-P-072, KC-P-069, KC-P-070, and KC-P-073, prepared according to Example 2 in the '098 patent, Examples 3 and 10 in the '358 patent, and Example 1 and Comparative Examples 1, 2, and 3 in the '617 publication, lack in purity compared to the purified stable Lansoprazole in claims 42-45 of the '535 application. The obtained Lansoprazole in the above identified samples contain 0.306%, 2.606%, 31.154%, 0.04%, undetected%, 0.055%, and an undetected% of the sulfone impurity respectively, and 1.843%, 21.875%, 40.378%, 34.431%, 10.038%, 61.040%, 98.693%, and 98.451% of the sulfide impurity respectively. In contrast, the purified stable Lansoprazole of the '535 application

contained less than 0.2% combined sulfone and sulfide impurities, particularly less than 0.1% of the sulfone impurity and less than 0.1% of the sulfide impurity.

16. Thus, in my opinion, the lansoprazole of the '535 application is a purified lansoprazole compared to the lansoprazole prepared according to the prior art '098 and '358 patents and the '617 publication.

IV. PREPARATION OF LANSOPRAZOLE ACCORDING TO THE '098 AND '358 PATENTS AND THE '617 PUBLICATION

17. I have directly supervised the stability experiments of the lansoprazole samples prepared according to Example 2 of the '098 patent (KC-P-067) and Example 1 of the '617 publication (KC-P-072). The lansoprazole samples prepared according to Examples 3 and 10 of the '358 patent, and Comparative Examples 1 - 3 of the '617 publication as described above were not included in the stability experiments considering the apparent lack of purity with respect to lansoprazole in those samples. These stability experiments of the purified lansoprazole samples are as follows.

18. The lansoprazole samples according to Example 2 of the '098 patent (KC-P-067) and according to Example 1 of the '617 publication (KC-P-072) were subjected to various storage conditions for a period of 3 months. These storage conditions are as follows; 3 months at 2-8°C; 3 months at ambient conditions (25°C) and a relative humidity of 60%; and 3 months at 40°C and a relative humidity of 75% (40°C).

19. Following storage, the impurity profile was determined using the HPLC USP method analysis for the examples obtained according to the various methods of preparing lansoprazole in the '098 patent and the '617 publication, as shown in Table 2.

Table 2: Impurity Profile of Lansoprazole Prepared According to the '098 patent and the '617 publication after storage for 3 months.

Reference		Visual Color	Total Impurity	Impurity profile in percent (w/w)					
				Impurity D	Impurity E	LNP-NO	LNP-SO_2	TFPB	LNP
US 4,628,098 Ex 2 (KC-P-067)	Time 0	White	2.15				0.031	1.84	97.85
	2-8°C	White	2.10				0.032	1.77	97.90
	25°C	Creamy	2.10				0.032	1.77	97.91
	40°C	Brownish	2.14		0.01		0.032	1.80	97.86
WO 01/21617 Ex 1 (KC-P-072)	Time 0	White	10.44			0.24	0.04	10.04	89.56
	2-8°C	White	11.30		0.14	0.23	0.03	10.69	88.70
	25°C	Creamy	11.01		0.39	0.22	0.03	9.99	88.99
	40°C	Brownish	12.37	0.04	1.04	0.15	0.06	10.65	87.63

Time 0 represents the impurity profile at 0 months of storage, 2-8°C the impurity profile following storage at 2-8°C for 3 months, 25°C the impurity profile following storage for 3 months at ambient conditions and a relative humidity of 60%, and 40°C the impurity profile following storage at 40°C and a relative humidity of 75%.

In the above table Impurity D, Impurity E, LNP-NO, LNP-SO_2, and TFPB represent the most common impurities of Lansoprazole, LNP-SO_2 being the sulfone impurity and TFPB the sulfide impurity.

20. It is my opinion, that in addition to lacking the recited purity both of the Lansoprazole samples KC-P-067 and KC-P-072 prepared according to Example 2 in the '098 patent, and Example 1 in the '617 publication, lack the stability compared to the purified stable Lansoprazole of the '535 application. The obtained Lansoprazole in the above identified samples shows discoloration to a creamy color upon storage for 3 months at ambient conditions at a relative humidity of 60% and a brownish color upon storage for 3 months at 40°C at a relative humidity of 75%, indicating degradation of the lansoprazole contained in the samples. Further, the amount of TFPB in the lansoprazole sample according to Example 1 of the '617 publication increases from 10.04 to 10.65% following storage for 3 months at 40°C and 75% relative humidity. In contrast, the purified stable Lansoprazole of the '535 application contained less than 0.2% combined sulfone and sulfide impurities,

particularly less than 0.1% of the sulfone impurity and less than 0.1% of the sulfide impurity and does not change color upon storage for a period of 3 months at 40°C and 75% humidity.

21. The lansoprazole of the samples prepared according to the Examples 3 and 10 of the '358 patent and Comparative Examples 1-3 of the '617 publication has a purity much less than the 0.2 % combined sulfone and sulfide impurities, particularly less than 0.1% of the sulfone impurity and less than 0.1% of the sulfide impurity and would for this reason alone lack the recited purity and stability limitations of the stable lansoprazole of the '535 application.

22. Thus, in my opinion, lansoprazole of the '535 application is a purified and stable lansoprazole compared to the lansoprazole prepared according to the prior art '098 and '358 patents and the '617 publication.

23. I declare that all statements made herein are true, and that all statements made herein on information and belief are believed to be true, and that all statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code, and that any willful false statement may jeopardize the validity of any United States Patent that would issued from the '485 application.

Dated: 7.10.2009 Signed: _____

Claude Singer, Ph.D.